Risk-Stratified Pharmacovigilance for Biosimilars in Saudi Arabia

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Abstract

Risk-stratified pharmacovigilance offers an efficient approach for the surveillance of biosimilars. It leverages available sources of data and minimizes the need for extensive additional post-marketing data collection. Saudi Arabia's biosimilar market has expanded in recent years, particularly for the treatment of autoimmune diseases and cancer. Nevertheless, although the country possesses an active pharmacovigilance system, further effort is necessary to establish a risk-stratified pharmacovigilance programme exclusively for biosimilars. (Omair et

al.2022) Risk assessment generally relies on data available through clinical trials, regulatory submission processes, or post-marketing surveillance (Bin Yousef et al., 2022). Recruitment of the relevant stakeholders – including manufacturers, regulators, healthcare professionals, and patients – is crucial, as is maintenance of the trust of the public in the pharmacovigilance infrastructure (Alharf et al., 2018). The collected data facilitate the prioritization of where the most effort should be channeled, and serve to concentrate the limited resources available on the most problematic biosimilars. In Saudi Arabia—currently exhibiting a rapidly growing biopharmaceutical industry—, is undertaking regulatory and institutional changes to effectively respond to the imminent biosimilar market. This presented article explores those factors and formulates a framework for a risk-stratified pharmacovigilance strategy. The proposal starts by conducting a preliminary review of the literature, followed by the establishment of a risk-assessment methodology; subsequently, data sources relevant to pharmacovigilance are characterized, and specific challenges of biosimilars in the Saudi Arabian context are discussed. A general overview of risk-stratified approaches follows, with a particular emphasis on the benefits of incorporating advanced analytic tools that augment traditional systems.

1. Introduction

The global market for biosimilars has grown markedly, now exceeding 50 approved products and trading at more than $13 billion per year (Oza et al., 2019). Saudi Arabia sees a similarly rapid increase: approximately 200 approved biosimilars are available to healthcare professionals, voluntarily or upon request, across many therapeutic classes. The Biosimilars Forum highlighted improper reporting of biosimilar adverse effects to pharmacovigilance programmes (Bin Yousef et al., 2022). Risk-stratified pharmacovigilance, a validated strategy for efficient monitoring, remains unexplored in the Saudi context.

Relying on worldwide databases, the Food and Drug Administration's post-marketing studies and surveys, and the World Health Organization's spontaneous adverse-event reporting systems, this work seeks to develop a risk-based strategy for pharmacovigilance in Saudi Arabia. Analysis of specific case studies, definitions of risk-assessment criteria, and identification of primary challenges and recommendations comprise the approach. The database is extensible and promises benefits when revisited, thanks to periodic revisions and re-assessments based on new regulations and developments. (Polkot, 2021)

2. Background on Biosimilars

Biosimilars are biologic medicines highly similar to reference products concerning safety, quality, and efficacy. Their development process includes proof-of-comparability activities designed to demonstrate similarity to the original reference (Oza et al., 2019). Biosimilars differ from generic drugs because parenteral administration is mandatory for these products; moreover, adverse reactions may differ due to the post-translational protein structure of these molecules, which can provoke immunogenic responses. Consequently, biosimilars cannot be regarded as generic medicines.

3. Pharmacovigilance: Definition and Importance

Pharmacovigilance, also termed drug safety monitoring, encompasses the science and activities linked to the detection, evaluation, understanding, and prevention of adverse drug reactions or any other drug-related issues (Oza et al., 2019). Compliance with good pharmacovigilance typically involves the reporting of all types of suspected reactions; drug interactions—either between drugs or between drugs and food; Adverse drug reactions (ADRs) associated with drug withdrawal; medication errors or overdose; and any lack of efficacy to regulatory authorities. Aggregate reports are also required, such as periodic safety update reports (PSURs) and risk management plans (RMPs). The PSUR plays a key role in the identification of new safety signals, the assessment of benefit–risk profiles, and the formulation of risk management strategies. The RMP details the risk management system necessary to identify, characterize, and minimize risks throughout a product's life cycle. Pharmacovigilance provides the tools to analyze and evaluate safety data from various sources such as clinical trials, registries, and spontaneous reports, and to implement effective risk minimization measures. In Saudi Arabia, pharmacovigilance has been identified as a critical factor to enhance post-market drug safety, with

analytical reports into the pattern of ADRs in patients specifically requested by stakeholders (Bin Yousef et al., 2022).

4. Current Landscape of Biosimilars in Saudi Arabia

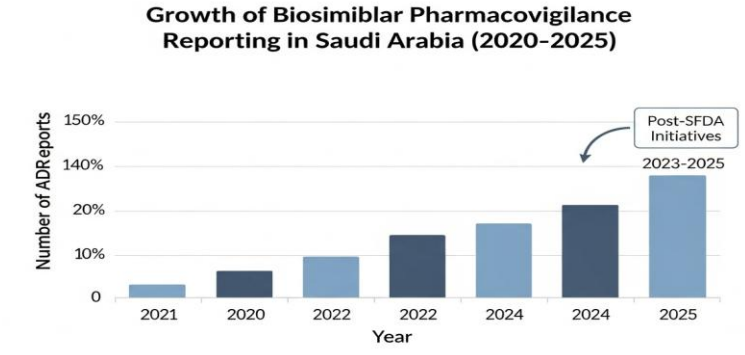
The first biosimilar pharmaceutical product in Saudi Arabia was Somatropin in 2006, followed by the second biosimilar, Filgrastim, in 2009. Since then, the introduction of biosimilars has accelerated, contributing to a clear decline in prices across all major pharmaceutical categories. Biosimilars account for approximately 4.8% of the pharmaceuticals consumed nationwide. These dynamics position Saudi Arabia distinctively compared to many other countries (El Zorkany et al., 2018). Saudi Arabia's healthcare system is the dominant player in biosimilar supply, presenting favorable prospects for biosimilar procurement.

5. Regulatory Framework for Biosimilars

The Saudi Food and Drug Authority (SFDA) adopts the International Conference on Harmonization (ICH) guidelines to regulate biosimilars marketed in the Kingdom. The guidelines require the submission of an abridged product information file supported with robust scientific evidence on quality, safety, and efficacy, in addition to good manufacturing practices licensing granted by a qualified regulatory body (M. Alhawassi et al., 2018). The SFDA mandates pharmaceutical companies to implement and maintain a pharmacovigilance system for all licensed products, including biosimilars. National regulations require submission of Adverse Drug Events (ADE) reports by concerned stakeholders within a stipulated timeframe. Supportive action plans, including risk minimization measures, must be initiated in response to regulatory feedback.

6. Methodology

This research used a multi-faceted approach to develop a safety monitoring framework for biosimilars in Saudi Arabia. The multi-faceted approach is based on study with a mixed-methods methodology and quantitative and qualitative data analyses. Research that informs this process began with an extensive review of the relevant evidence base of scientific literature that informed the risk assessment approach. The research also used comprehensive review of existing data from other sources; for example, data from global databases, post-marketing studies of the United States Food and Drug Administration (USFDA), and spontaneous adverse-event reporting by the World Health Organization. To develop the method, the research used the multi-faceted study approach to address the overarching objectives of the study. These objectives included understanding the data sources relevant to pharmacovigilance; conducting a detailed analysis of the case studies regarding specific biosimilars (e.g., rituximab and etanercept) to review their efficacy/safety profiles in Saudi Arabia; and reviewing the issues relevant to biosimilar pharmacovigilance in Saudi Arabia, specifically the challenges of data quality, engagement with stakeholders, and public trust. The research also considered and reviewed the regulatory environment in Saudi Arabia, looking to see whether any reforms might be possible in this space. The synthesis of these analytical components culminates in the formulation of a structured framework for a stratified pharmacovigilance process, aimed at applying resources proportionally to the risk metrics of the market in Saudi Arabia.



7. Risk Assessment Methodologies

Risk assessment plays a critical role in pharmacovigilance in Saudi Arabia (Alharf et al., 2018). Effective assessment informs policy and resource allocation and directs monitoring efforts toward areas of heightened concern. Risk stratification enables adaptation to the evolving pharmacovigilance landscape, which increases the volume of reported adverse events and the diversity of implicated products. Risk assessment approaches fall into two broad categories: qualitative and quantitative (Bin Yousef et al., 2022). Qualitative methods utilize descriptor data and expert judgment to characterize risk, while quantitative methods apply mathematical or statistical tools to raw data. Several methods use a combination of both quantitative and qualitative techniques. (EFSA et al.2022)

Saudi Arabia's regulatory framework for biosimilars guides the application and acceptance of analytical tools, with emphasis on measurably demonstrated predictive value, interpretability, and transparency.

7.1 Qualitative Risk Assessment

Qualitative risk assessments usually produce relative measurements of the risk for given process or product. They help evaluate the likelihood of occurrence and the expected impact on goals. Preliminary risk evaluations based either on experience and expertise or on data from literature are considered as qualitative assessments. Such approaches are recommended for screening and prioritizing risks for further analysis and provide a basis for the selection of further steps towards risk management.

7.2 Quantitative Risk Assessment

Quantitative risk assessment involves numerical estimation that helps in the evaluation of a potential risk. When only a limited data is available, the resulting estimates tend to be debatable. In the case of context safety, these assessments can be used to estimate the effects of releases and the impact of subsequent exposures. Saudi Arabia requires quantitative estimates of risk for the Quantitative risk assessments (QRA) element, but relevant guidance is available to manage this requirement (Bin Yousef et al., 2022). QRA have become common-place in many countries, and QRA methods are described and explained in several international standards, notably BS 8800. By incorporating extensive generic botanical data, regulatory mandates, dose-related effects, and an analysis for pre-existing conditions, quantitative risk assessment can aid in the prediction and prevention of adverse drug events (A. Almubark et al., 2020).

8. Data Sources for Pharmacovigilance

Pharmacovigilance operates through signal detection, validation, study, and finally the reduction or removal of risks to medicinal products. These processes are informed by data from numerous sources including clinical trials, versus real-world non-clinical practice, as well as spontaneous reporting systems. Clinical studies, despite their designation as the gold standard, do not always reflect current clinical practice. Study outcomes are often based on specific patient cohorts, and market exposure is frequently limited by selected patients and artificial study parameters. Consequently, there is increasing reliance on post-marketing surveillance to both reinforce and supplement clinical trial information. This reliance is especially important for biosimilars, whose approval process requires demonstration of comparable efficacy and safety to pioneer biological medicines, and thus have been extensively tested in clinical trials prior to market entry. (Jeon et al., 2024)

8.1 Clinical Trials Data

Clinical trials data represent a critical source for pharmacovigilance, providing pre-marketing safety information used to identify the potential adverse effects of medicines that inform risk assessment. As a key instrument in risk assessment, clinical trials data can be used for the development of risk-based stratification approaches to pharmacovigilance that consider the extent of available safety information and help direct appropriate risk-management decisions (Bin Yousef et al., 2022). A detailed review of clinical trials conducted in Saudi Arabia further highlights the value of clinical trials data as an input to risk assessment for risk-stratified pharmacovigilance. Saudi Arabia deploys a significant number of bioequivalence trials to assess the safety of generic drugs, integrated within a bioequivalence framework that ensures quality standards and safeguards patient health (A. Althunian et al., 2024).

8.2 Post-Marketing Surveillance

Post-marketing surveillance (PMS) has a significant role in pharmacovigilance, which is a process dedicated to the detection, broad evaluation, and prevention of any potential adverse effects of prescription drugs. It is considered a mandatory process worldwide and corresponds to risk screenings of medicines on a broader scale. PMS data comes primarily from pharmaceutical companies, healthcare professionals, and consumers via various channels such as social media, scientific publications, prospective and observational studies, and randomized controlled trials. These data generate signals designed to increase the level of urgency that trigger comprehensive risk assessments and the establishment of remedial actions (Bin Yousef et al., 2022).

Several forms of PMS can be adopted; data collection approaches which can passive, retrospective, or spontaneous collection or can be actively collected in the form of prospective studies. Forms of spontaneous reporting range from direct reporting in a filed ADR report to reporting via social media platforms such as Twitter and Facebook. The Uppsala Monitoring Centre (UMC) publishes standards and protocols dedicated to PMS, such as the UMC Structured Terminology (UMC-ST) and the Common Terminology Criteria for Adverse Events, which help in cataloging both serious and non-serious adverse effects (Alharf et al., 2018).

8.3 Spontaneous Reporting Systems

Spontaneous reporting is a common source to collect data on ADRs for analysis. Studies that use these data often use the term “spontaneous reports” or “spontaneous adverse event reports” interchangeably. Spontaneous reporting is a pharmacovigilance system that allows health professionals, manufacturers, and consumers to report suspected ADRs associated with marketed drugs. Several regulatory agencies have established and support spontaneous reporting systems worldwide: the USFDA supports the Vaccine Adverse Event Reporting System (VAERS) and the Adverse Events Reporting System (FAERS); Health Canada supports the Canadian Vigilance Program; the Pharmacovigilance Programme of India maintains the Vigibase and the Vigiflow; the European Medicines Agency uses the EudraVigilance system; and the UK Yellow Card Scheme is run by the Medicines and Healthcare products Regulatory Agency (Alharf et al., 2018). Because only a single volcanic event of an ADR or no event is large enough to generate a signal, other than unexpectedly frequent events, most national pharmacovigilance centers analyze these data qualitatively to identify emerging safety issues. Spontaneous reporting on drugs launched in the market by authority plays a crucial role in pharmacovigilance; the Saudi Vigilance Program, established in 2009, designed a suitable mechanism to encourage healthcare professionals to report serious ADRs that were observed within the health system. (Khardali, 2024) (Shanableh et al., 2024).

Pharmacovigilance allows the identification and notification of new, rare, and serious ADRs of medicines in the post-marketing phase. It should involve a multi-stakeholder effort and the participation of major stakeholders within the medicine-use system. The implementation of a national pharmacovigilance system should integrate clinical, scientific, managerial, operational, organizational, and governmental aspects in the countries, because pharmacovigilance is a growing science in accelerated growth, requiring adequate resources of personnel, funds, services, training, and implementation (Bin Yousef et al., 2022).

9. Challenges in Pharmacovigilance for Biosimilars

Biosimilars in Saudi Arabia offer improved access to cost-effective treatments. Pharmacovigilance is critical to ensure their safety and traceability and to enhance patient confidence. Propelled by this context, a risk-stratified strategy to pharmacovigilance is designed by mapping the biosimilar life cycle, identifying risk factors, and combining multiple risk assessment methods to allocate effective tools and resources over time. This approach is also applicable to other regions. In Saudi Arabia, the uptake of biosimilars is expected to increase as soon as six more products are added to the Positive List for Insurance Reimbursement Warehouses (PFI-ReWare), which is issued semi-annually by the Ministry of Health (MOH). Despite their relative novelty, biosimilars account for no less than 18% of biological procurement volumes in the MOH central and regional warehouses. To support this trend, a national program to promote biosimilar uptake in public sector hospitals would enhance both

system efficiency and patient access (Bin Yousef et al., 2022). With over 30 biosimilars on the Saudi market, risk-stratified pharmacovigilance can serve as complementary regulatory guidance, helping to ensure public health and preserve patient confidence (Alharf et al., 2018). Pharmacovigilance during the national transition is recommended to mitigate the risk of significant uptake across the private healthcare sector that operates without formulary restrictions. The shortage of quality data, particularly at the national level, constrains the ability to assess the relative importance of pharmacovigilance challenges. Overcoming the three main challenges identified previously would mitigate the others. Complying with Global Good Pharmacovigilance Practice necessitates material support to the National Pharmacovigilance and Drug Safety Centre (Saudi Vigilance) from the SFDA, such as dedicated offices for major hospitals (Niazi, 2023).

9.1 Data Quality Issues

Ensuring data quality is fundamental for creating an effective pharmacovigilance programme since defective data—such as incomplete, inaccurate, untimely, or misleading information—could lead to improper decision-making. Presently, several issues related to data quality (mainly in spontaneous reporting) are limiting the ability to analyze and extract meaningful conclusions for risk assessment. Previous studies in Saudi Arabia have observed under-reporting, inaccurate filling of the reporting form, limited knowledge and awareness about pharmacovigilance, and lack of appropriate training among healthcare professionals (Bin Yousef et al., 2022). Although some of these issues are for the local pharmacovigilance system in general and not related specifically to biosimilars, the pharmacovigilance system might be struggling to provide actionable information related to these medicines due to scarcity of clean and complete data. It is therefore important that these issues be comprehensively addressed before considering risk-based monitoring for biosimilars. A national center that collects, analyses, and releases drug-safety data should take the lead in coordinating data-improvement strategies. (Albertsdóttir, 2022)

9.2 Stakeholder Engagement

Stakeholder engagement involves actively participating and understanding the viewpoints of individuals or organizations that influence or are influenced by specific initiatives. In pharmacovigilance, it is essential to identify the key players who can impact activities and understand the roles played by various stakeholders in this field. These stakeholders include manufacturers, regulators, healthcare providers, patients, and the general community.

The Saudi Vigilance program, established in 2009 by the SFDA, is a case in point. This program was developed to monitor public health by addressing pharmacovigilance activities. Since its inception, the pharmacovigilance system has undergone significant improvements, demonstrated by initiatives such as the development of guidelines, enhancement of communication and reporting tools, staff training, and the encouragement of stakeholders to comply with the program's requirements (Alharf et al., 2018). These diverse initiatives have been vital in effectively improving the pharmacovigilance system in Saudi Arabia. Successful programs must also proactively engage the community; Saudi Arabia faces the challenge of enhancing stakeholder engagement and public trust to ensure a comprehensive pharmacovigilance system.

9.3 Public Perception and Trust

Pharmacovigilance faces challenges related to data quality, stakeholder involvement, data accessibility, and public trust that undermine effective monitoring (Alkhalidi et al., 2019). Greater awareness and engagement among health care professionals, patients, and the public are essential. Improving knowledge and reporting of ADRs strengthens the system; eight in ten patients who experience ADRs fail to report them, with only 66% of pharmacists exhibiting adequate ADR awareness (Farhat et al., 2016). The implementation of risk-stratified pharmacovigilance depends on safeguarding consumer trust, which is often low due to limited mandatory reporting and minimal use of structured methods such as prescribing, dispensing, and screening safety information systems for signal detection.

10. Case Studies of Biosimilars in Saudi Arabia

Biologic agents represented 16.4% of the Saudi market in 2018 (El Zorkany et al., 2018). Fourteen biologics have been approved by the SFDA and

marketed in Saudi Arabia, with an average of 42.9% of the usage being attributed to biosimilars. There is no maximum limit on the biosimilar uptake in Saudi Arabia. At the same time, many pharmaceutical companies have been encouraged to develop more biosimilars for the Saudi market to contain the increasing cost of pharmaceuticals and improve patient access to biologics. Another factor supporting the increase of biosimilar use is the Saudi Vision 2030 that encourages investing in the biologics sector.

The literature review showed a large number of biosimilars that were introduced in Saudi Arabia. The most used biosimilars include adalimumab, bevacizumab, etanercept, infliximab, trastuzumab, pegfilgrastim, rituximab, and filgrastim. However, the available literature does not provide a detailed insight into the Saudi market penetration of each individual biosimilar product. (Batran et al., 2022)

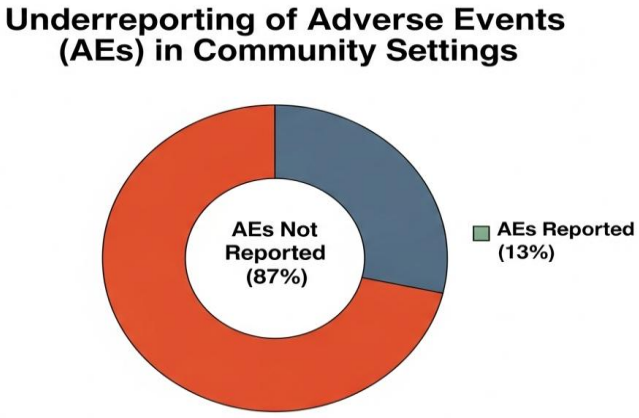
10.1 Efficacy and Safety Profiles

The two selected case studies—rituximab (reference product and biosimilar) and etanercept (biosimilar)—provide valuable insights into the efficacy and safety profiles of biosimilars authorized in Saudi Arabia. Both biosimilars have been approved by the SFDA, the EMA, and the USFDA. The rituximab biosimilar treatment was initiated in Saudi Arabia in mid-2020, whereas the etanercept biosimilar has not yet been adopted in clinical practice as of early 2022. Worldwide sales of rituximab biosimilars are projected to reach $12.2 billion by 2026, accounting for 30% of total sales across emerging markets and EU-5 (United Kingdom, Italy, Germany, France, and Spain).

The rituximab case study is particularly informative because it permits detailed monitoring and exploration of the strengths and weaknesses of the pharmacovigilance framework for biosimilars in Saudi Arabia. Post-marketing safety and efficacy data are available for both the biosimilar and the reference product, facilitating direct comparisons and informed decision-making. Conversely, the etanercept case study underscores the challenges of evaluating efficacy based solely on data from the reference product. This scenario highlights the current limitations in the routine application of pharmacovigilance for biosimilars in Saudi Arabia and the need for comprehensive data collection once the biosimilar enters the local market (Bin Yousef et al., 2022).

10.2 Adverse Event Reporting

The underreporting of adverse events (AEs) is a pervasive issue worldwide even after the establishment of pharmacovigilance systems and policy development (Bin Yousef et al., 2022). A study carried out by Almubark et al. (A. Almubark et al., 2020) showed that 87% of the participants did not report their AEs within the community setting in Riyadh, Saudi Arabia. A study conducted in the United Arab Emirates suggested non-committal behavior as the primary cause of underreporting AEs. Pharmacists in community pharmacies play a significant role in pharmaceutical care as well as in educating patients about the safe and proper use of prescribed medicines. The underreporting of AEs by community pharmacists has been recognized as a contributing factor to this problem. Encouraging community pharmacists to report AEs is essential to enhance pharmacovigilance activities and thereby reduce subsequent hospital admission due to AEs.



11. Risk-Stratified Approaches to Monitoring

Risk-stratified pharmacovigilance enables regulators and decision makers to concentrate resources on products that potentially pose significant risks and minimizes the monitoring of low-risk products that are unlikely to cause clinically important safety issues. This approach is not intended to replace existing pharmacovigilance processes but rather to segment the system where the level of effort expended is commensurate with the likely level of risk. Risk stratification relies heavily on the availability of standardized, high-quality data as well as the methods and means for analyzing the data accurately and meaningfully even when the information is incomplete or sparse. Risk-stratified pharmacovigilance frameworks incorporate a variety of data sources including spontaneous reporting schemes and prior knowledge, supported by quantitative and qualitative risk-assessment tools. Such approaches have been developed and applied to selection of dose, additional risk-reduction measures, and benefit–risk evaluation. These support decisions on the further development of medicines and whether their licenses should be renewed. (Lin et al., 2023)(Eastham et al.2022)

The study objectives were therefore to establish a framework for risk-stratified pharmacovigilance of biosimilars in Saudi Arabia, generate guidance on its effective application, identify the principal biosimilars in the Saudi pharmaceutical market and health system, analyze current and predicted utilization patterns, assess specific risks and develop targeted approaches for their surveillance, and examine the regulatory context and the potential for legislative reform to support efficient and risk-based pharmacovigilance (Bin Yousef et al., 2022).

11.1 Tailored Surveillance Strategies

Tailored surveillance strategies represent a cost-effective solution to monitoring biosimilars, recognizing that a risk stratification approach is not mandatory for every biosimilar product.

A risk-stratified framework considers product, patient, and prescriber factors to establish the necessary intensity of pharmacovigilance for a specified period, facilitating evidence generation for effective and cost-efficient biosimilar oversight. Furthermore, ongoing targeted risk communication can optimize information dissemination related to pharmacovigilance activities and issues pertinent to specific biosimilars or their classes (Bin Yousef et al., 2022).

11.2 Targeted Risk Communication

Communication plays a vital role in maintaining the safety of pharmacotherapy in Saudi Arabia. Targeted risk communication not only delivers the right information to the right recipient, but it also affects the actions of healthcare providers in either initiating or discontinuing actions that may affect patient safety (Bin Yousef et al., 2022). Building on risk assessment, risk communication serves as a cornerstone of effective safety assurance. Communicating the low level of residual risk of biosimilars, along with the overall positive observations and benefits for the community, helps generate a balanced sense of awareness. Pharmacovigilance efforts employ different communication methods contingent on the national health infrastructure and stakeholders' capabilities, availability, and preferences. The choice of an effective channel is as critical as the information itself; the channel must be continuously monitored, and if it becomes ineffective, alternative channels are promptly explored. Documentation constitutes an essential component of outreach. Furthermore, the same communication channel may not be uniform for different recipients. Targeted communication for a pharmacist, physician, or patient plays a supporting role in appropriately implementing and utilizing the safety information (M. Malebari et al., 2020). Parallel to pharmacological or pharmaceutical considerations, biosimilars are introduced as innovative products characterized by enhanced safety, sustainability, and community health benefits. The communication approach should factor in these attributes. From a Saudi perspective, targeted risk communication should address correctly and clearly the following aspects: (a) low residual risk, (b) knowledge for safe utilization, (c) implications and regulations surrounding patient switching, (d) contamination and batch effect, (e) invalid substitution, (f) traceability, (g) stability and storage conditions, (h) product authenticity, and (i) cancer risk.

12. Integration of Technology in Pharmacovigilance

Risk-stratified pharmacovigilance offers a more efficient and cost-effective strategy, when compared with routine pharmacovigilance. The integration of

artificial intelligence (AI) and big data analytics therefore enables better insights and solutions for risk stratification (Alharf et al., 2018).

12.1 Artificial Intelligence

Modern pharmacovigilance faces a growing influx of data, including social media and various internet sources (M. Kassem et al., 2021). This steady increase in information opens the door to AI and machine-learning approaches that might automate or assist current procedures. Through AI, pharmacovigilance staff could quickly sift through numerous ADR reports to extract relevant information on the benefit–risk characteristics of medicinal agents (Danysz et al., 2018). Currently, the primary data-processing task involves the triage of incoming reports, where AI could benchmark new submissions against similar cases or existing knowledge obtained from literature, textbooks, and comparable drugs (Liang et al., 2022). The assessment of relevance, which leads to either expedited follow-up or routine database archiving, is a natural testbed for automation. Furthermore, the detailed evaluation of a report's importance to the associated medicinal product could be automated, primarily by matching case details to known ADR patterns. As the industry and regulators accumulate vast datasets comprising millions of individual case safety reports (ICSRs), AI tools become essential for the manageable and swift identification of significant cases. AI could also aid Risk Management Plans (RMPs) by generating testable hypotheses without human oversight, predicting the granular, real-world development of numerous potential risks, and directing focus towards the most pertinent concerns. It might identify safety signals inconspicuously embedded within routine safety data. Moreover, AI may serve as an agent for signal validation by assembling auxiliary quantitative and qualitative evidence, evaluating the quality and plausibility of generated signals, and rendering recommendations regarding scientific validity and importance. AI can also extend its assistance to literature screening, fielding signals, automatic drafting, and regulatory submission processes.

12.2 Big Data Analytics

Big data analytics involves extracting, transforming, and organizing high-volume, high-variety, and high-velocity data for analysis. The significance of big data analytics is evident in the capability of optimized facilities to extract relevant information from extensive employee data and subsequently explore knowledge to refine the modelling system. In the business domain, big data analytics addresses challenges related to large-scale service analysis by consolidating big data for insightful and strategic outcomes. Big data analytics distinguishes itself from traditional data analysis through its reliance on algorithms capable of autonomous execution, facilitating deeper and timely analytics, thereby unveiling concealed anomalies untouched by conventional analytic methodologies (Alharf et al., 2018).

13. International Best Practices in Pharmacovigilance

International pharmacovigilance of biosimilars is developing worldwide at a varied pace, with regulatory approaches in the mid- to long term expected to reach more vigorous and standardized levels. Saudi Arabia exhibits a highly developed and growing infrastructure in pharmaceutical regulation and dare the early lead in introducing international best practices.

Eight categories have stirred international regulations in the field of biosimilars. These include: quality and safety, stability studies, commercial guidelines, scientific advice and biosimilar development, intellectual property, clinical aspects, indication extrapolation, and pharmacovigilance. Yet, international best practices often remain complementary to formal regulatory pharmacovigilance, and partly overlap with more routine legislative rules dedicated to marketing-authorization holders or producers. Nonetheless, the Saudi Arabian regulatory framework regards these areas as mandatory components of the biosimilar oversight.

Saudi pharmacovigilance fully supports the recent introduction of international best practices that incorporate biosimilars within the "general rules concerning post-authorization safety studies applicable to medicinal products" that are available on the SFDA's Pharmaceutical Vigilance guidelines for safety monitoring (Alharf et al., 2018). The biopharmaceutical strategy includes the specific wording that reflects this enhancement by defining an additional category for routine post-authorization safety studies that are allowed to meet additional requirements (depending on the national or regional need and Assessment Reports National Institute of Public Health): "where pharmacovigilance or risk minimization activities can be targeted on the basis of a Risk Assessment for the benefit–risk of the medicinal product estimated more precisely" (Bin Yousef et al., 2022). Demands for more refined post-marketing safety-monitoring methods are forthcoming.

13.1 Comparative Analysis with Other Countries

Saudi Arabia's risk-stratified pharmacovigilance framework for biosimilars contrasts with other countries' provisions. In general, setting guidelines for signal generation, evaluation, and risk minimization activities faces two recurring caveats: (a) differences between biosimilars and their original biologics in terms of structure and manufacturing processes make systematic comparison problematic; and (b) the considerable lack of safety data on individual biosimilars for an approach based upon the pre-existing experience with the original biologic may generate signals where there is no actual increased risk (Bin Yousef et al., 2022). Furthermore, even when a biosimilar undergoes head-to-head comparisons, regulatory agencies often do not systematically request sufficient evidence to quantify and characterize remaining uncertainties. Those gaps require careful consideration and further reflection on the methodological foundations of risk stratification and risk quantification needs. Some agencies, however, already recommend risk-adapted approaches to post-marketing oversight of biosimilars. Such adaptive frameworks frequently include internal company procedures to address requests on risk management and pharmacovigilance plans (A. Althunian et al., 2024). These features are conspicuously absent from the Saudi Arabian context. Nonetheless, the country is likely amenable

to the adoption of a cost-effective risk-stratified framework tailored to the relevant factors influencing the introduction and use of biosimilars in its healthcare system.

13.2 Lessons Learned

A reinforced understanding of biosimilars articulates the necessity to adapt monitoring procedures. The principal of biological agents, which are stratified into included and non-included agents, offer a means to categorize risk levels. Included principal agents encompass anti-TNF-α agents, G-CSFs, erythropoietin-stimulating agents, insulin and its analogues, somatropin, and follitropin alfa. Penicillamine, fingolimod, cyclophosphamide, and interferons are also grouped within the included category. Conversely, non-included principal agents include abatacept, rituximab, and bevacizumab in addition to mycophenolate mofetil, tacrolimus, and cyclosporine (A. Althunian et al., 2024) (Bin Yousef et al., 2022). This delineation hinges on the purity and heterogeneity of the active substance.

14. Policy Recommendations for Saudi Arabia

The increasing clinical adoption of biosimilars–is expected to result in an unintended increase of adverse drug reactions stated for the originator product. Recent incidents pointed towards insufficient pharmacovigilance systems worldwide, especially in the developing countries. Such scenarios indicate an immediate demand for the development of risk-based pharmacovigilance systems capable of ensuring the detection of possible issues and ensuring patient safety. Drawing on qualitative, quantitative, and mixed methods, this article develops a framework for a stratified pharmacovigilance process aimed at applying resources proportionally to the risk metrics of the market of Saudi Arabia.

Pharmacovigilance monitors, assesses, and averts adverse drug reactions that originate from inadequate efficacy or unforeseen side effects (M. Alhawassi et al., 2018). The unique characteristics of biosimilars extend the scope of pharmacovigilance systems, making it a fundamental instrument for regulation and enhanced observance, both during clinical trials and medical practice (Bin Yousef et al., 2022).

14.1 Strengthening Regulatory Framework

The Kingdom of Saudi Arabia (KSA) has created a robust landscape for the regulation, authorization, and surveillance of innovative medical products. Similar governance structures have been applied to biosimilars, now an essential component of efforts to improve access to quality medications and contain healthcare costs. Biosimilars require specific monitoring arrangements because their development and manufacturing methods differ from the originators. Risk-stratified pharmacovigilance is therefore under development in Saudi Arabia as the preferred framework for comprehensive evidence assessment and surveillance.

Among pharmaceutical products, biologics and their biosimilars attract ongoing attention in many countries. Broad familiarity with the target active pharmaceutical ingredient (API) may exist from extensive toxicological testing of a related molecule; however, final safety profiles may nevertheless

remain uncertain. The endocrinology division of the US Anesthesia Patient Safety Foundation has warned that biologics can pose "uncertain risks," indicating that "patient data are limited, and space capsules have better reliability than our existing knowledge of biologics." Hence, these products as a distinct pharmaceutical category merit targeted monitoring.

Monitoring of biosimilars is especially important because these biological products are manufactured with living systems (e.g. cell lines) and can thus differ slightly from one another even though they contain closely similar amino acid sequences. In Saudi Arabia, recent policy initiatives to further a 2030 vision for advancing pharmaceuticals and patient safety have therefore recommended establishment of a clear and transparent mechanism for patients and healthcare providers to report quality issues related to generic and biosimilar medicines. A fast-track approval process for new medications should also be introduced alongside a national health outcomes research center for carrying out observational studies of the quality of medications in general and biosimilars in particular (M. Alhawassi et al., 2018). The ability to cope with regulatory dilemmas such as accelerated approval pathways, biosimilar manufacturing, control of API and excipient quality, pharmacovigilance, and combating counterfeiting will become increasingly important in this context.

14.2 Enhancing Training and Education

Training programs are key elements in a risk-stratified strategy. Biosimilar pharmacovigilance begins with awareness and knowledge among health professionals, patients, and manufacturers. A high level of understanding helps all these people to become more involved and aware of their roles and responsibilities. Conscious, attentive healthcare professionals and patients will report low-grade adverse events, improving the quality and quantity of post-marketing reports. Saudi pharmacists have limited knowledge of ADRs (Cheema et al., 2019). To create commitment, the roles and competencies of all relevant pharmacovigilance stakeholders should be defined clearly and communicated effectively.

The National Pharmacovigilance Centre at the SFDA could strengthen its function by developing a formal strategy for training all pharmacovigilance stakeholders that is aligned with principles identified in the 2009 pharmacovigilance guidelines. To ensure broad knowledge and involvement of the pharmacovigilance system, these training activities should include healthcare professionals, manufacturers, patients, academic institutions, and the National Pharmacovigilance Centre itself (M. Alhawassi et al., 2018). The high turnover of healthcare professionals in Saudi Arabia necessitates regular, cost-effective and convenient training.

15. Future Directions in Biosimilar Pharmacovigilance

The evolution of pharmacovigilance for biosimilars continues at a rapid pace domestically and internationally. National drug regulators, professional associations, academia, and policy experts in Saudi Arabia remain committed to fostering a fit-for-purpose post-marketing monitoring system. Progress in this endeavor relies on data and insights emerging from multifaceted projects, including the present study, exemplars of local biosimilar development, and evidence attained through routine commercial utilization. Scholarly research continues to develop innovative frameworks for risk assessment; initiatives employing qualitative, quantitative, or composite methodologies to prioritize resources and activities are particularly promising. Meanwhile, post-marketing studies furnish rich feeds of real-world evidence underpinning risk management programs. Development of methods and models to leverage current technologies, particularly in descriptor generation and digitization, holds potential to reduce reliance on resource-intensive, retrospective dossier analyses (Oza et al., 2019). Integration of extensive benefits data alongside adverse event reports can contribute to integrative risk-benefit analyses (Bin Yousef et al., 2022).

The consistent pursuit of further progress is evident across multiple areas. Specifically, biosimilar development remains nascent in Saudi Arabia: deepening and broadening the adoption of locally produced products, while concurrently managing natural attrition in initial approvals, will be instructive. Pilot initiatives explicitly designed to enhance targeted surveillance activities have yet been attempted. Considered engagement with the broader healthcare community in this process

appears desirable, particularly, for instance, when confronting complex switch scenarios such as immunogenicity. The potential of artificial intelligence to enhance both routine and extraordinary pharmacovigilance through real-time signal detection and prediction is attracting sustained attention. Stakeholders must therefore uphold regulatory arrangements to facilitate the accelerated introduction of beneficial innovations. The surge of new products and experiences generated by the COVID-19 pandemic established a major testbed for handling safety issues and furnished benchmarks for future reference.

15.1 Emerging Trends and Technologies

Advanced analytics and AI address challenging questions that go beyond traditional biostatistical methods and methods featured in the previous section. Advanced analytics and AI provide precise, context-dependent models that illuminate complex behaviors and outcomes. Although still emerging, these techniques operationalize previously inaccessible predictive patterns, enabling enhanced risk-stratified pharmacovigilance.

Healthcare systems and governments benefit from AI as it takes the post-marketing safety of new products to an unprecedented level. The widespread adoption of big data analytics continues, making advanced techniques more accessible. Parallel advances in computational resources and hardware, often in the form of cloud platforms, facilitate the construction, training, and deployment of deep neural networks, rendering intelligent approaches more practical in limited computational environments such as drug-safety monitoring. These technical trends provide a wide pool of possibilities and exciting avenues for improving both the accuracy of predictions and the design of high-impact experimental systems in post-marketing safety.

Pharmacovigilance programs face an ongoing need to update guidelines, invest in staff training, monitor international initiatives, upgrade systems, and develop tools that maintain a positive risk-benefit balance in pharmaceutical products. Looking ahead, national authorities develop guidelines for risk-benefit evaluation and risk minimization, complementing existing regulatory requirements and supporting risk-minimization systems (Alharf et al., 2018).

Data from routine pharmacovigilance case reports can be evaluated through a variety of methods that differ in the requirements for clinical expertise, time, and quality of output. Post-marketing safety activities ensure that manufacturers remain vigilant and effective in all these areas and that investigators and medical assessors are sufficiently familiar with the items contained within the individual risk-management plan. When used in conjunction with risk communication and key-message development, risk-stratified approaches enable manufacturers and regulators to focus resources on identified risks, facilitate detailed pharmacovigilance on products representing the most risk, and provide targeted summaries of the current safety profile to physicians (Bin Yousef et al., 2022).

15.2 Potential Research Areas

Despite the various biosimilars present on the Saudi market and the extensive information available on their safety, effectiveness, and immunogenicity, numerous research opportunities exist for risk-stratified pharmacovigilance. The risk of substituting a biosimilar for the original product remains a focal point for many researchers, clinicians, and regulators in Saudi Arabia (Alharf et al., 2018). A critical inquiry involves understanding the parameters that should be integrated into a risk-stratified approach to biosimilar regulation in the region. Insights on global models could inform Saudi policy, emphasizing the necessity for a bespoke stratification protocol tailored to local economic, academic, and healthcare delivery conditions (Bin Yousef et al., 2022). Successful deployment of such an approach also depends on delineating roles among the SFDA, healthcare regulators, and providers, ensuring comprehensive oversight of the biosimilar lifecycle. Furthermore, a knowledge assessment could identify informational deficits among prescribers, manufacturers, and other stakeholders, while comparative analyses between the Saudi and EU markets on uptake and adverse event reporting would illuminate areas for improvement.

16. Conclusion

Biosimilars have expanded the treatment armamentarium while offering cost savings, but uncertainty regarding their safety profiles remains. Risk-stratified approaches to pharmacovigilance can enable targeted safety monitoring and address this uncertainty while optimizing resource allocation. Although biosimilars require robust pre-approval clinical studies, post-marketing surveillance must also be sought since adverse drug reactions may be rare or delayed. Saudi Arabia has yet to widely adopt risk stratification in pharmacovigilance. As biosimilar uptake grows, bespoke workflows will further improve mortality and morbidity by guiding their appropriate use and ongoing safety monitoring.

Pharmacovigilance activities in Saudi Arabia could benefit from greater centralization, as the current regulatory environment requires each marketing authorization holder to establish an in-country pharmacovigilance contact point, with additional safety reporting requirements from the SFDA. Streamlining and centralizing some reporting activities would reduce redundancy and facilitate multi-stakeholder collaboration. Adjustable reporting frequencies and work sharing on causality assessment between local representatives and external safety officers based in the country would also improve the efficiency of pharmacovigilance (A. Althunian et al., 2024).

Clear regulatory frameworks and provision for supplemental testing and diverse sources of real-world data have encouraged biosimilar uptake in many therapeutic domains. Although healthcare practitioners and stakeholders have shown an inclination to prescribe and administer biosimilars, many require reassurance about their safety and efficacy, an area where pharmacovigilance plays an important role. Guidelines conforming to international best practice and tailored specifically to the Saudi Arabian context would help to consolidate confidence and enhance the transition from original biologics. The public sector, in particular, should promote awareness campaigns and incentives that spur greater prescription and administrative uptake, which would also encourage spontaneous reporting of adverse drug reactions (Bin Yousef et al., 2022).

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